OPPORTUNISTIC INFECTIONS

Dr. Dennis Rubel

Medical Director,

Themba Lethu Clinic

Right To Care

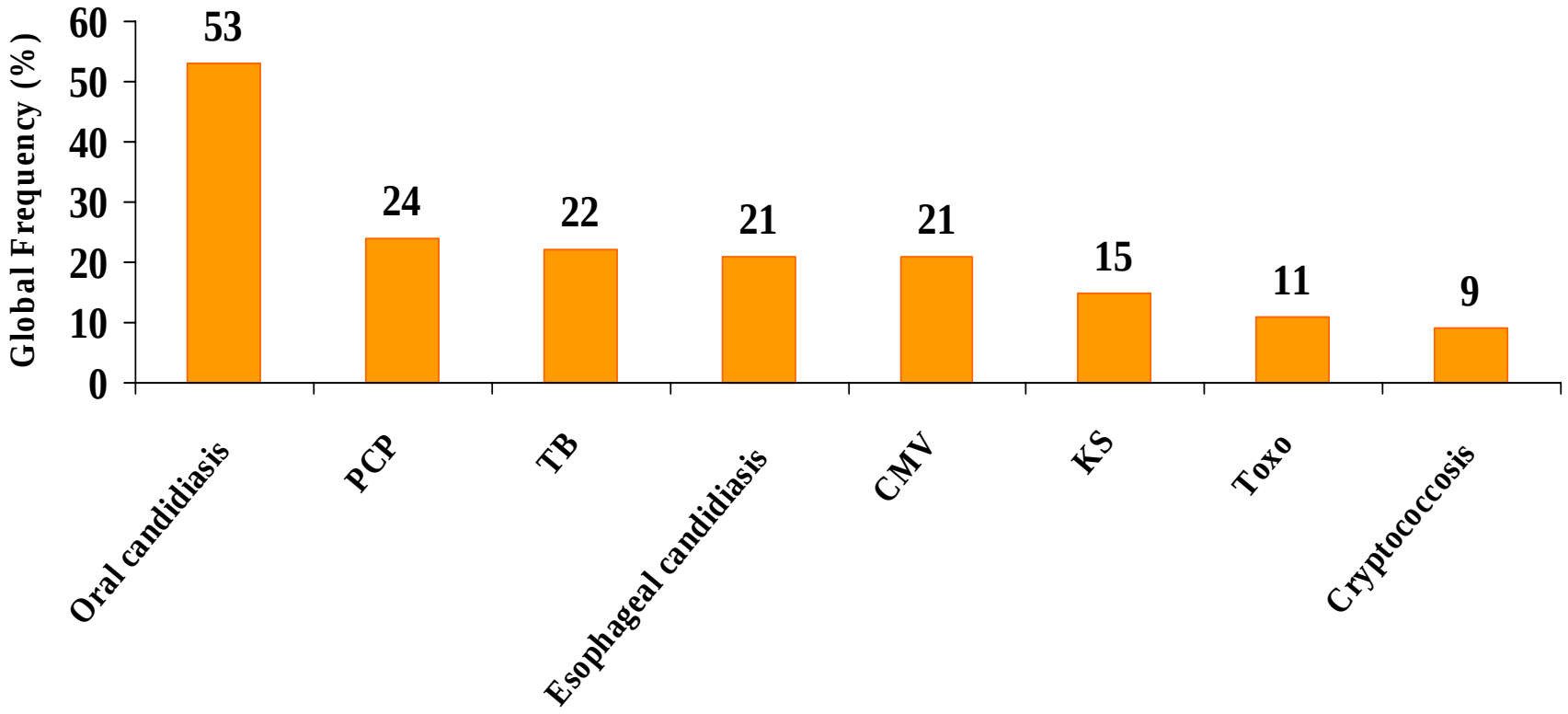
OPPORTUNISTIC

"the art, policy, or practice of taking advantage of opportunities or circumstances often with little regard for principles or consequences"

THE 5 MOST IMPORTANT OIs

1. TB
2. TB
3. TB
4. TB
5. TB

Most Common HIV-Related Conditions Globally

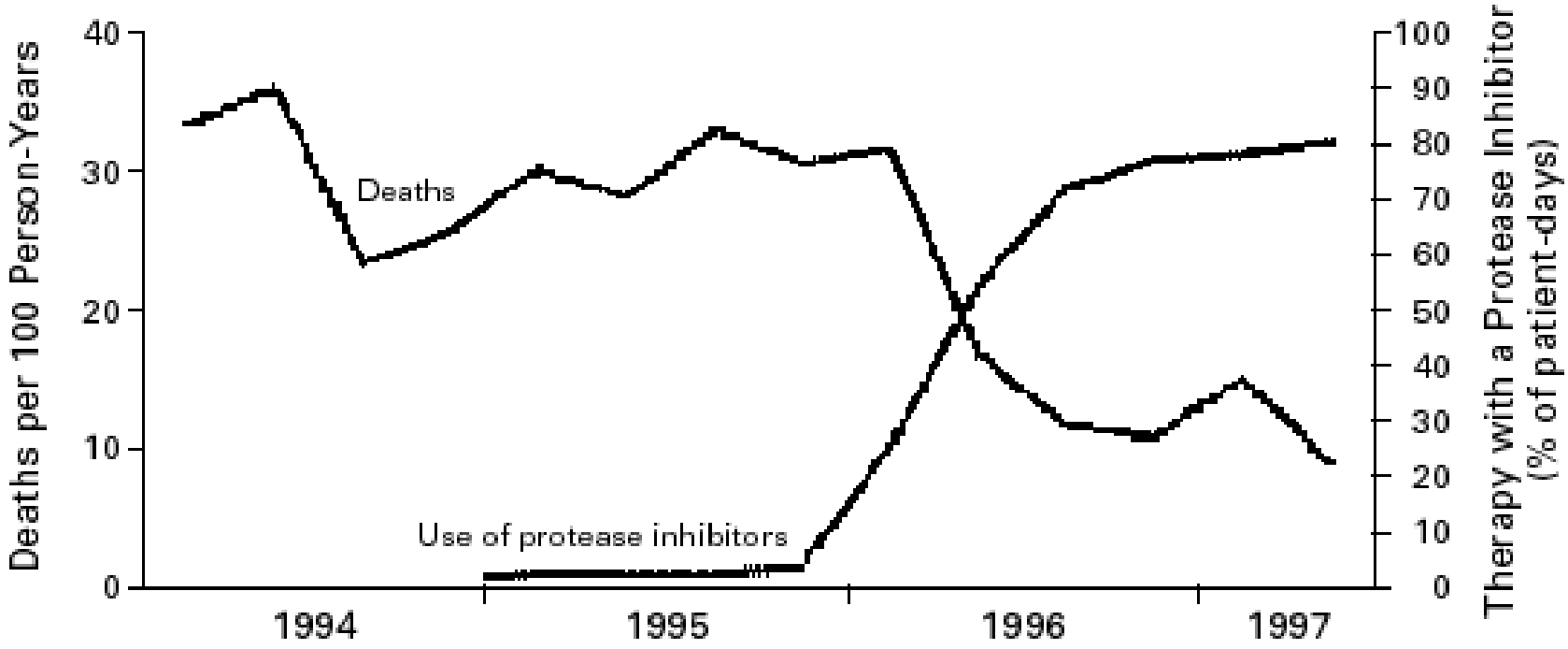


Access to drugs. UNAIDS Technical Update. October 1998

Distribution of complications associated with HIV/AIDS in medical wards at KEH in 2000

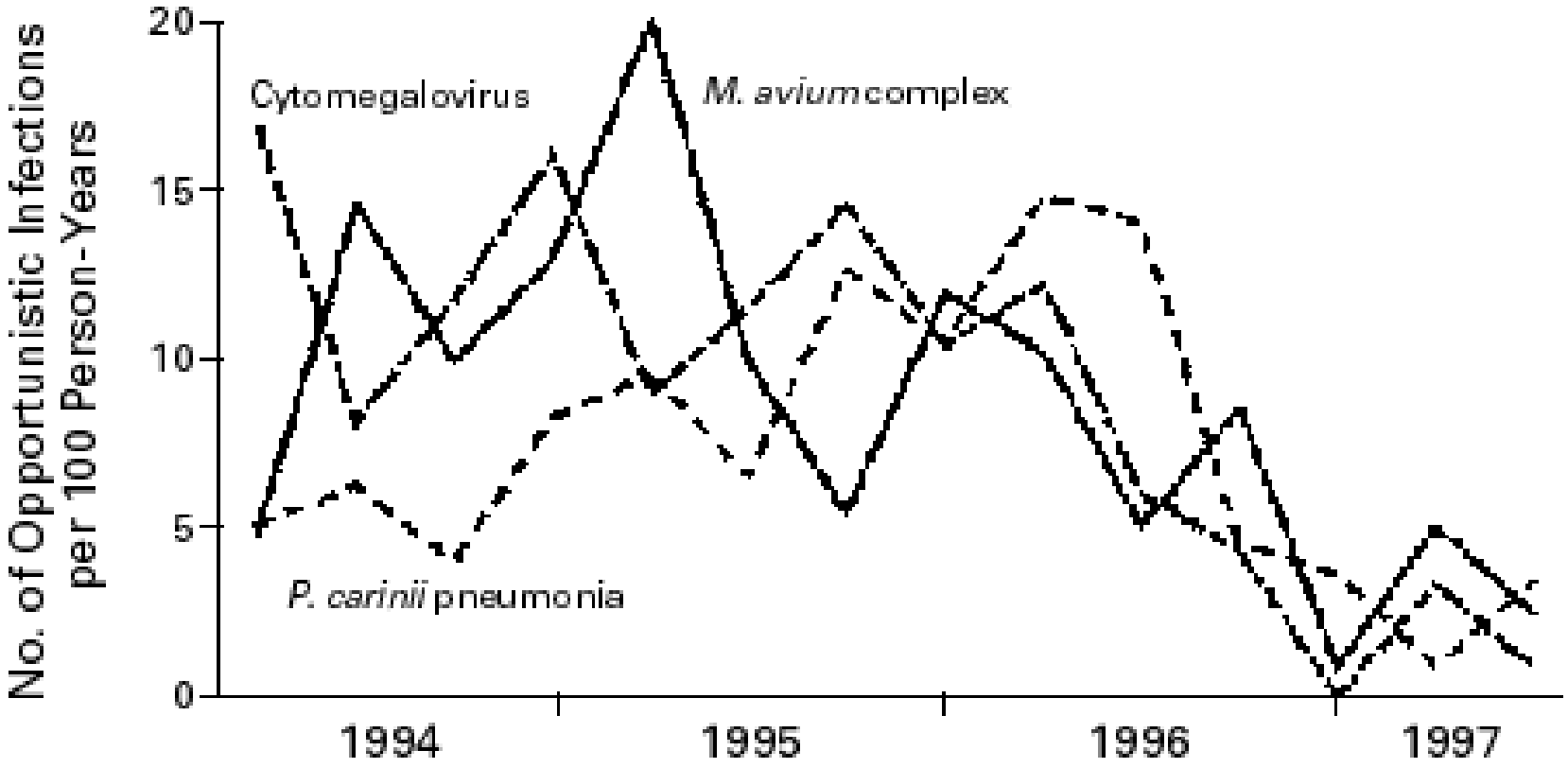
Tuberculosis	**1582**	**46.9 %**
◦ **pulmonary**	**1362**	
◦ **meningitis**	**163**	
◦ **pericardial**	**57**	
Enteritis	**423**	**12.5 %**
Oral candidiasis	**409**	**12.1 %**
Bacterial pneumonia	**364**	**10.8 %**
Pneumocystis pneumonia	**171**	**5.1 %**
Cryptococcal meningitis	**156**	**4.6 %**
Pancytopaenia	**49**	**1.4 %**
HIVAN (Nephropathy)	**51**	**1.5 %**
Kaposi's sarcoma	**49**	**1.4 %**

Impact of HAART on mortality in USA



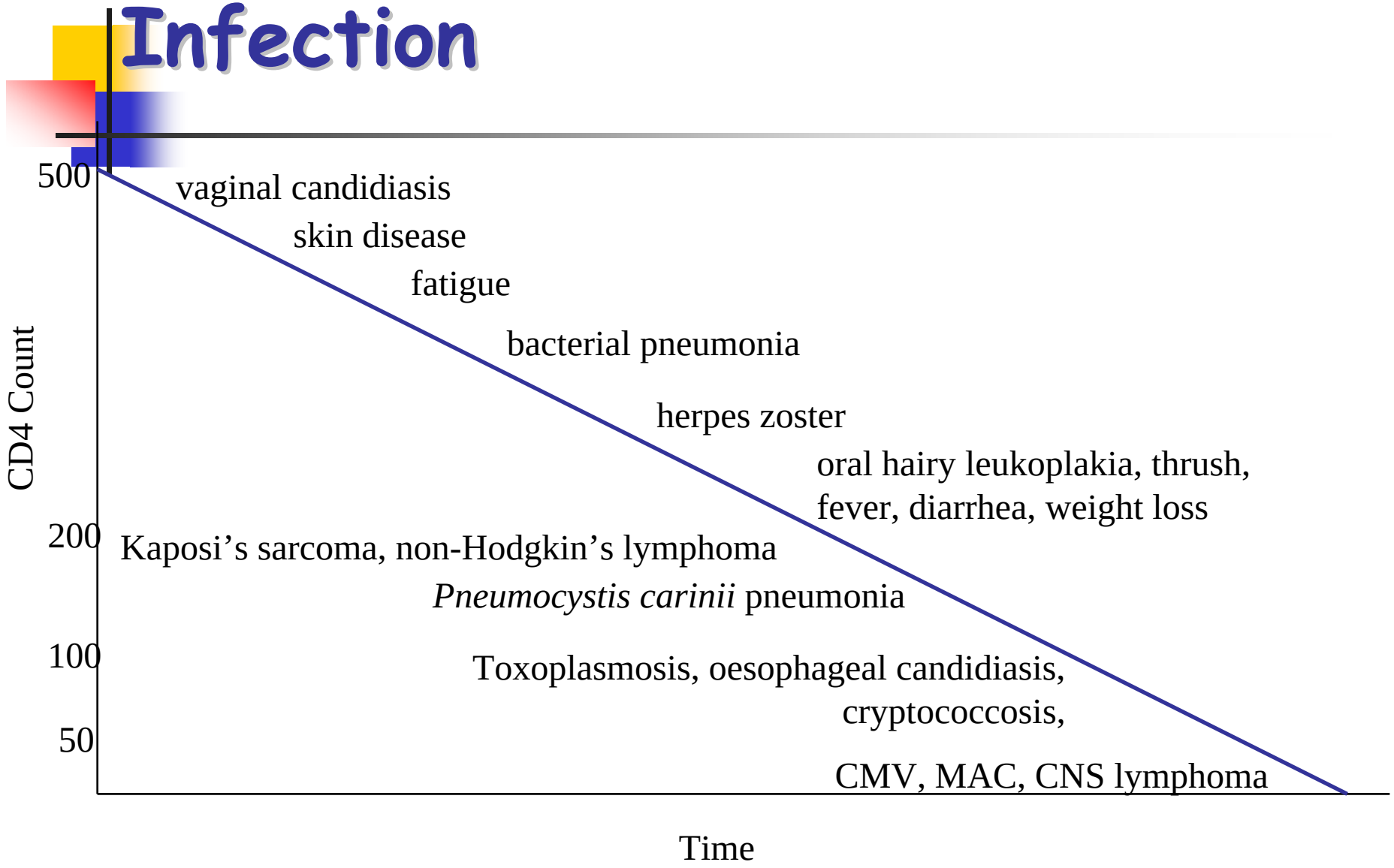
Palella et al , NEJM 1998

Impact of HAART on OI morbidity in USA



Palella et al , NEJM 1998

Natural History of HIV Infection



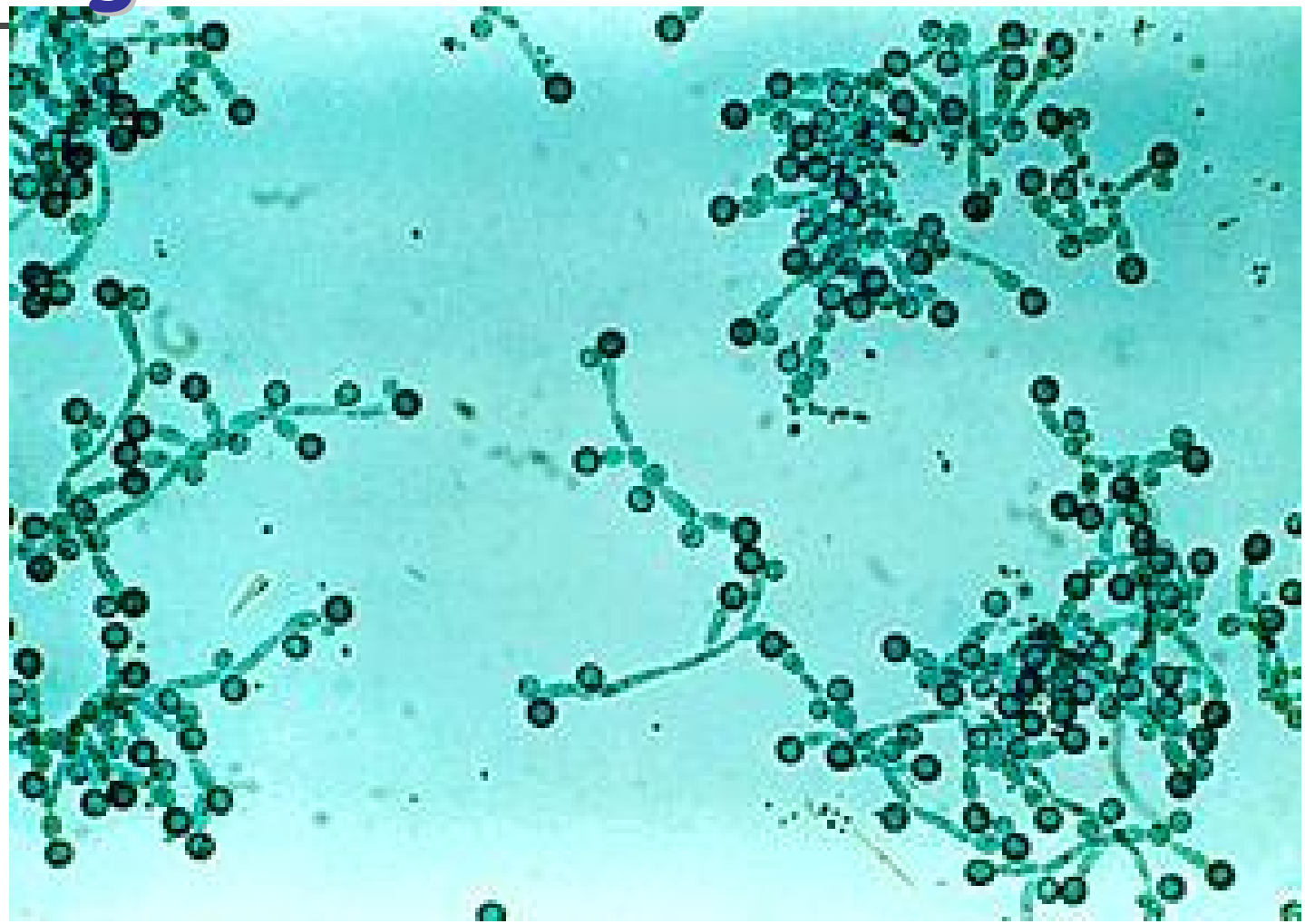
Candidiasis

- Almost exclusively mucosal
- Oropharyngeal candidiasis occurs in 74% of HIV-infected patients
- 1/3 recurrent; more severe as immunodeficiency advances
- Oesophageal involvement is reported in 20 to 40% of all AIDS patients

Diagnosis of candidiasis

- Fungal cultures rarely required
- Scraping of a lesion: characteristic spherical budding yeasts and pseudohyphae (KOH preparation or gram stain)

Diagnosis of candidiasis

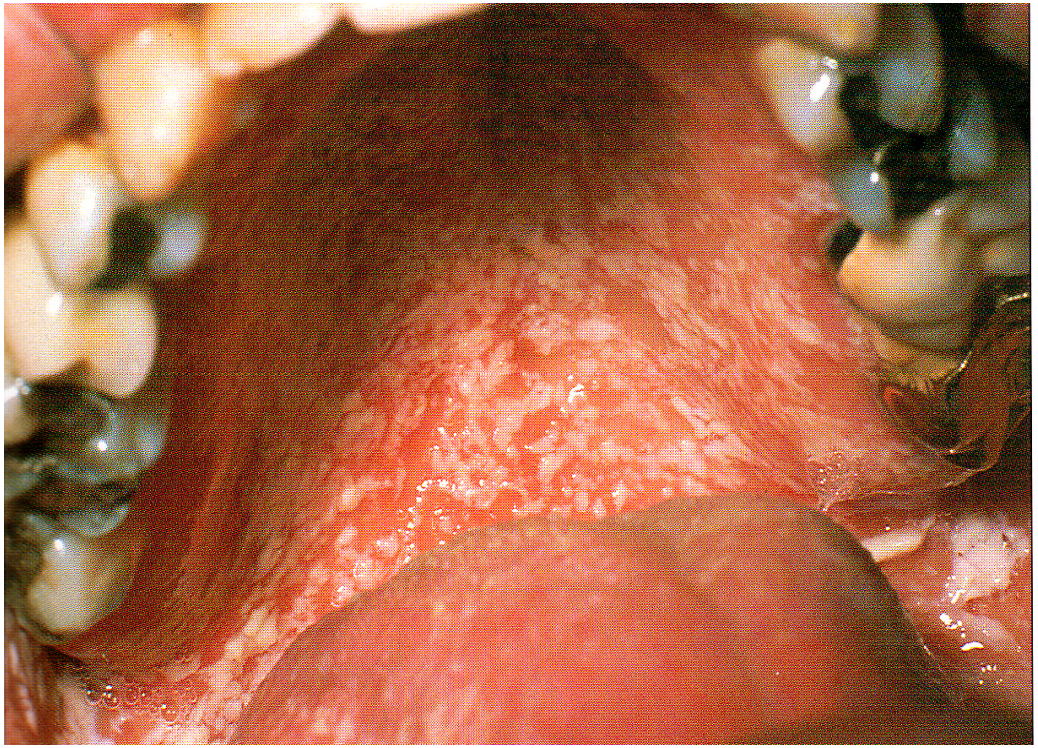


Pseudomembranous (thrush) type

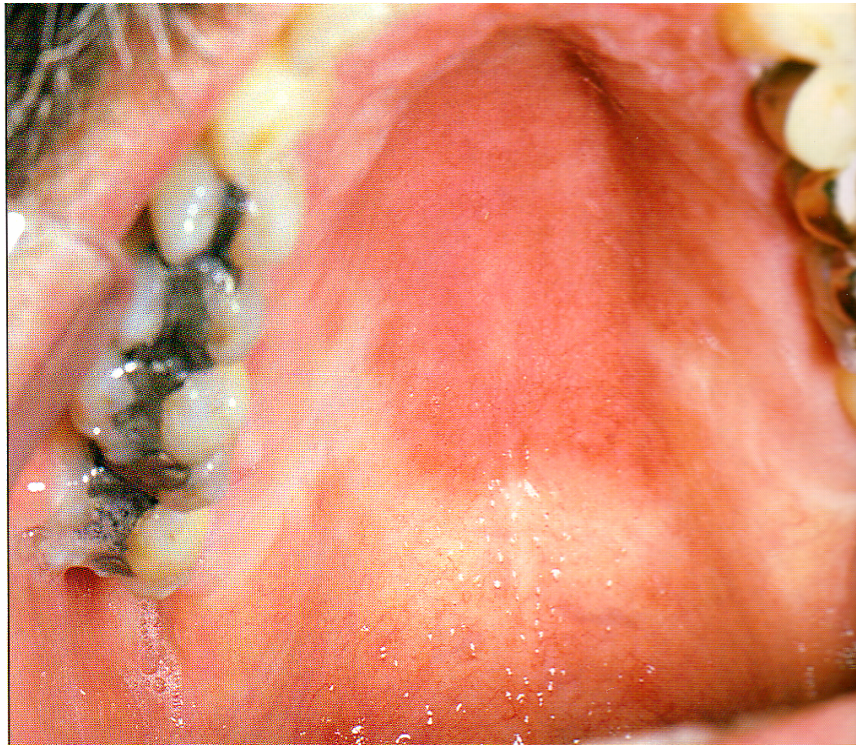
Erythematous (atrophic) type

Hypertrophic type

Oropharyngeal Candidiasis



Pseudomembranous candidiasis (thrush)



Erythematous candidiasis

Clinical features of oral candidiasis

- Most patients are symptomatic and may complain of some oral discomfort
- 4 forms of oral lesions:
  - pseudomembranous
  - erythematous (or atrophic)
  - hypertrophic
  - angular cheilitis

Clinical features of oesophageal candidiasis

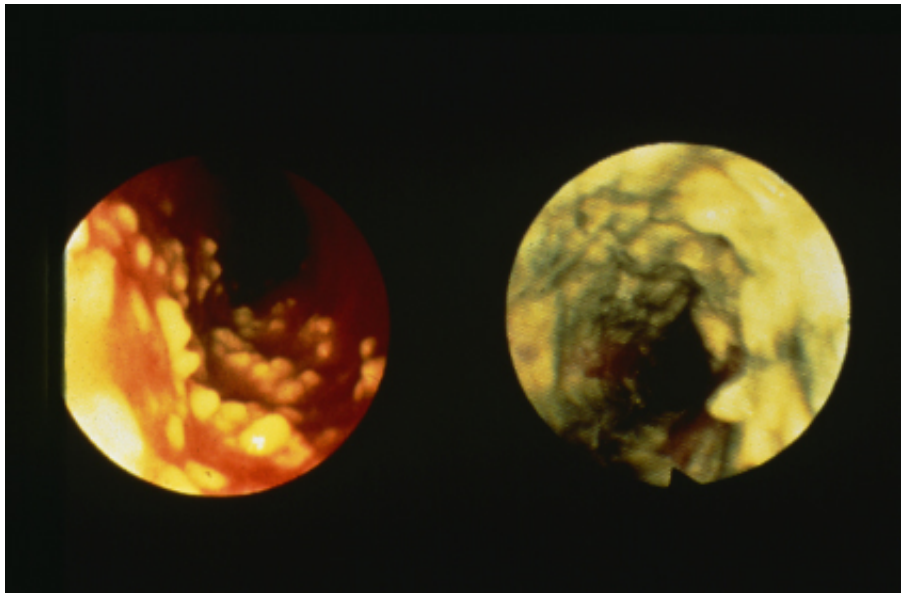
- Dysphagia or odynophagia
- Oesophageal lesions: pseudomembranes, erosions, and ulcers
- Visible oral candidiasis + oesophageal symptoms = oesophageal involvement

Clinical features of oesophageal candidiasis

- Treat empirically with antifungal therapy
- Endoscopy reserved for:
  - those patients who fail to respond
  - to evaluate for the presence of other diagnoses (e.g. HSV or CMV esophagitis, idiopathic ulceration)

Oesophageal Candidiasis – Initial Infection

- *Preferred*
  - **Fluconazole** (200mg/d po up to 400mg po/d)
  - Fluconazole clinically superior to ketoconazole
  - Treat for 2 wks



Clinical features of vaginal candidiasis

- Most patients present with vaginal itching, burning or pain and vaginal discharge
- Examination of the vaginal cavity reveals thrush, identical to that seen in the oropharynx

Treatment of vulvovaginal candidiasis

- Initial episodes are managed readily with topical therapy (clotrimazole, miconazole, or butoconazole)
- Systemic therapy is rarely needed for uncomplicated cases
- Fluconazole single dose of 150 mg orally is an alternative

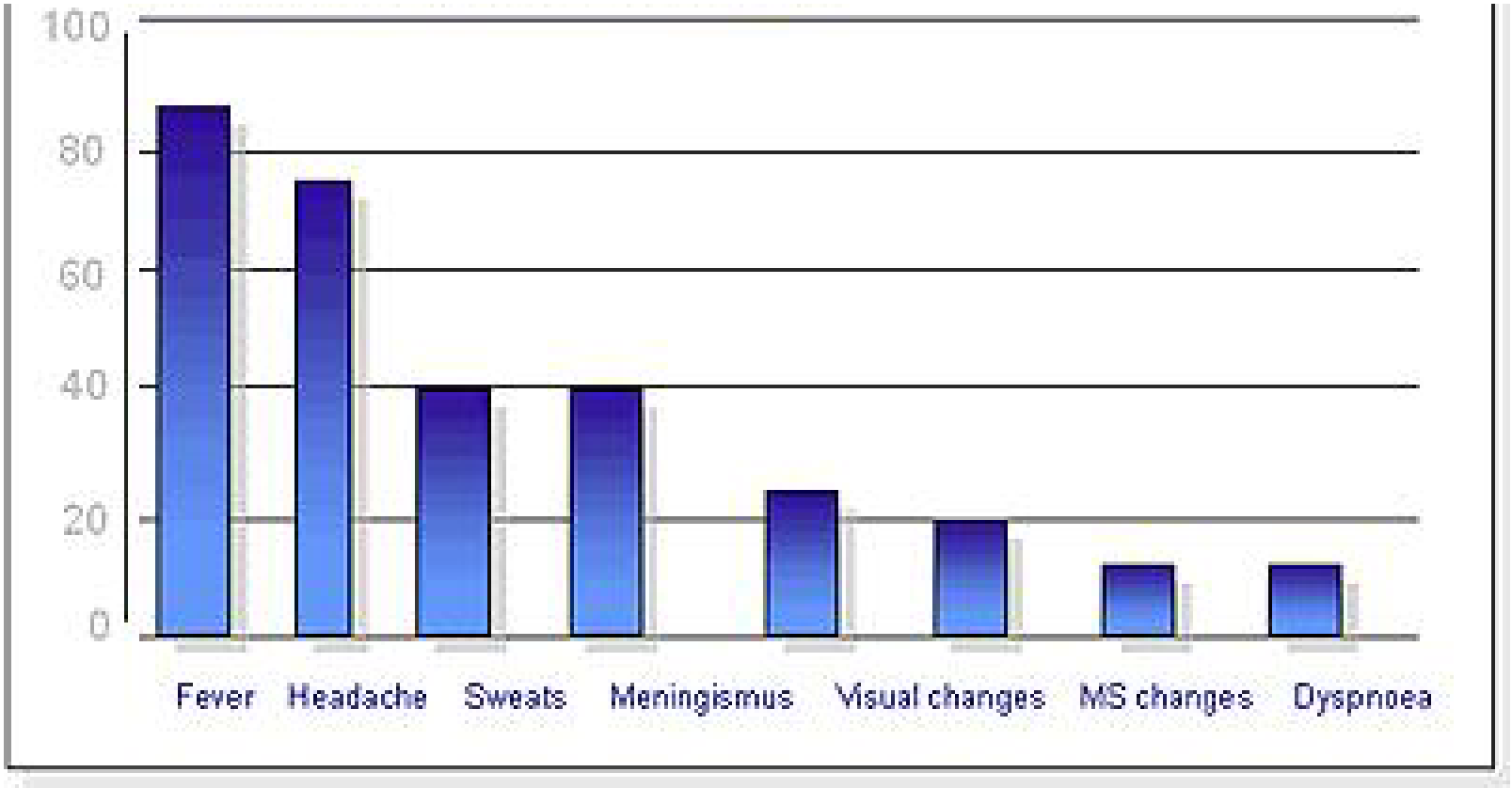
Cryptococcal Meningitis

- Cryptococcal meningitis has become the commonest cause of meningitis in adults in many African settings
- Prognosis without treatment is poor and even with anti-fungal treatment mortality remains substantial.
- ARV treatment is essential in altering the risk profile

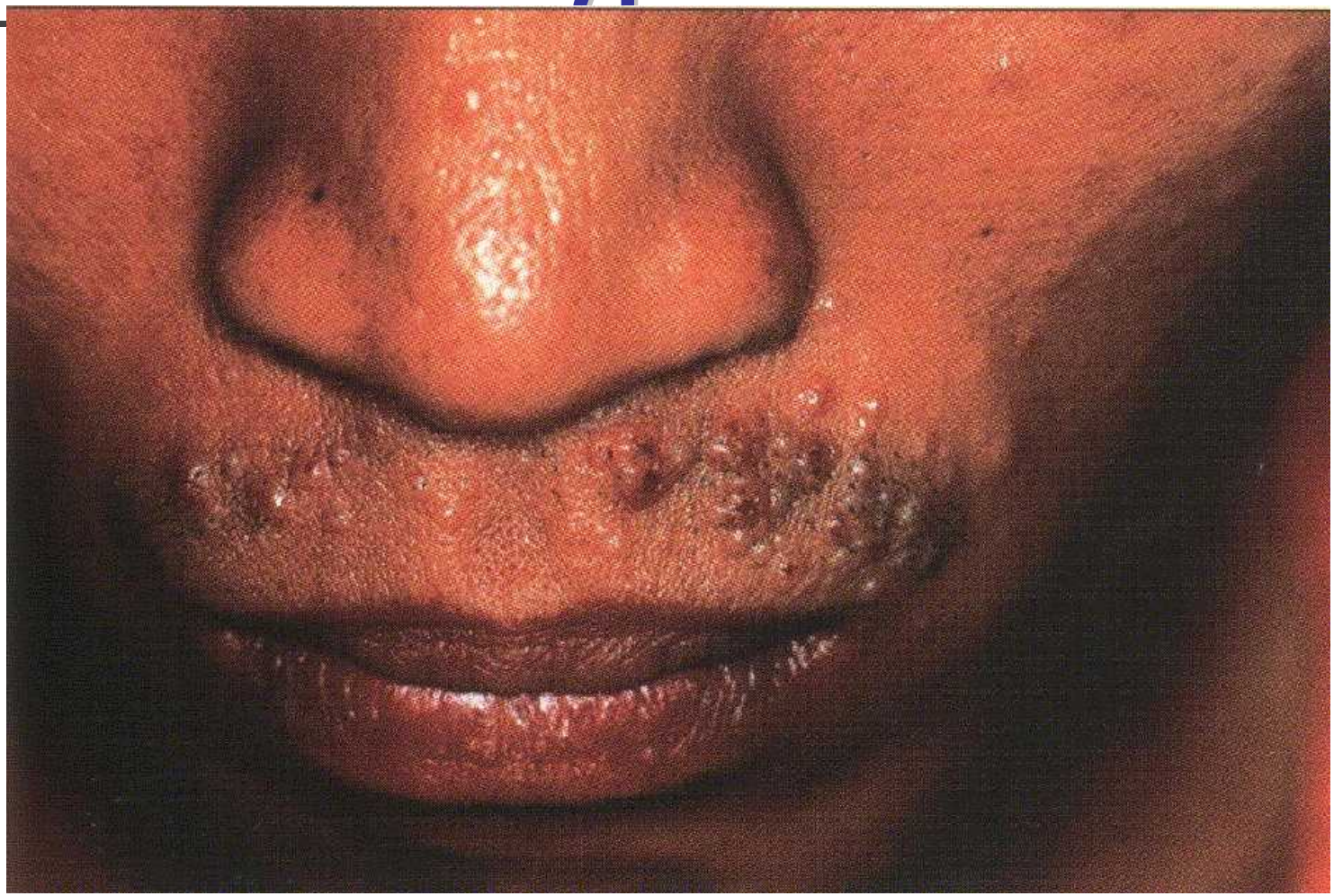
Cryptococcosis

- Virtually all HIV-associated infection is caused by *C. neoformans* var. *neoformans* (serotypes A and D)
- Most cases are seen in patients with CD4 <50 cells/mm^3
- acute primary infection vs. reactivation of previously dormant disease?

Clinical features of cryptococcosis



Cutaneous cryptococcosis



Diagnosis of cryptococcosis

- CSF: mildly elevated protein, normal or slightly low glucose, a few lymphocytes, and numerous organisms
- Cryptococcal antigen is almost invariably detectable in the CSF at high titer
- Opening pressure is elevated in up to 25%: important prognostic and therapeutic implications

Cryptococcal Meningitis Lab Investigations

- Gold standard for crypto meningitis: +ve CSF culture
- Blood fungal culture is +ve in 66-80% of patients with AIDS vs. 33% of HIV-ve patients
- Extra-neural Crypto diagnosed by tissue exam
- CT scan (done for exclusion of SOL e.g. toxoplasmosis or lymphoma)
  - shows brain atrophy and ventricular enlargement. Rarely mass lesions seen

Diagnosis of cryptococcosis

- Cryptococcal antigen in the serum is highly sensitive and specific for *C. neoformans* infection
- Positive serum cryptococcal antigen titer >1:8

Cryptococcal Meningitis

Treatment of acute infection

Drug(s) of first choice:

- Amphotericin B 0.7 mg/kg/d IV +/- flucytosine 100 mg/kg/d x 10-14 days
- then fluconazole 400 mg bid x 2 days, then 400 mg/d x 8-10 wk or itraconazole 400 mg/d x 8-10 wk

- Alternatives:
  - Fluconazole 400 mg/d x 6-10 wk
  - Itraconazole 200 mg tid x 3 days, then 200 mg bid x 6-10 wk
  - Fluconazole 400 mg/d plus flucytosine 100 mg/kg/d x 6-10 wk

Cryptococcal Meningitis

Suppressive therapy

- Drug of first choice: Fluconazole 200 mg up to 400 mg/day
- Alternatives:
  - Amphotericin B 0.6-1 mg/kg 1-3x/wk
  - Itraconazole 400 mg/d or 200 mg oral suspension/d

Prophylaxis (CD4 <50)

- Drug of first choice: Fluconazole 200 mg/d
- Alternative: Itraconazole 200 mg/d or 100 mg oral suspension/d

Cryptococcal Meningitis

- Patients treated with ARVs and CD4 >100-200/mm^3 for >= 6 months: discontinue prophylaxis

Cryptococcal meningitis - Other management issues

- Focal neuro signs or obtundation: CNS imaging before LP
- If opening pressure > 250mm H20, CSF drainage until <200 or 50% of OP; repeat LP daily until stable
- LP at 2 weeks to see if CSF sterile. If not may need longer induction phase

Cryptococcal Meningitis Course & Prognosis

- Even in treated patients mortality can be as high as 30%
  - although some series have reduced this to 6% with aggressive therapy
- Baseline factors associated with poor prognosis are:
  - Altered mental status
  - High fungal burden-high CRAG titers, +ve India ink, presence of extra-neural cryptococcal disease
  - Elevated intracranial pressure

Pneumocystis Carinii Pneumonia (PCP)

- incidence increasing
- 20% in a local study
- insidious
- acute
- atypical presentations

PCP

- Infection when CD 4 < 200 /ul
- Insidious onset illness
- Fever, dyspnoea and cough
- May be asymptomatic
- Extrapulmonary manifestations

Clinical features of PCP

- Insidious onset illness
- Symptoms may be present for weeks
  - Fever, DOE, cough, haemoptysis rare
  - 6-7% asymptomatic
- Occasionally presents as acute fulminant infection
- Signs
  - Tachypnoea and fever common
  - Rales and rhonchi in only 30-40%

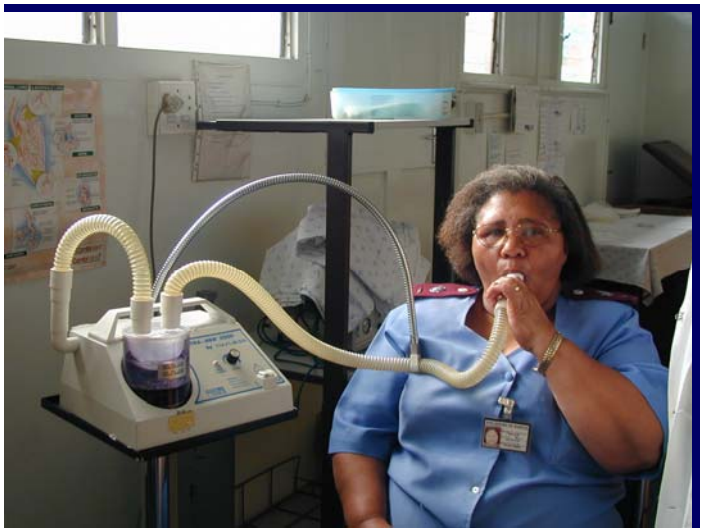
Laboratory features

- LDH reflects disease severity
- Advanced immunosuppression
  - CD4 < 200
- Hypoxia common but may be absent

PCP

Diagnosis of PCP

- Need a sensitive, reliable and non-invasive tool for early detection and diagnosis
- Standard procedure
  - Induced sputum
  - Bronchoalveolar lavage
    - histology



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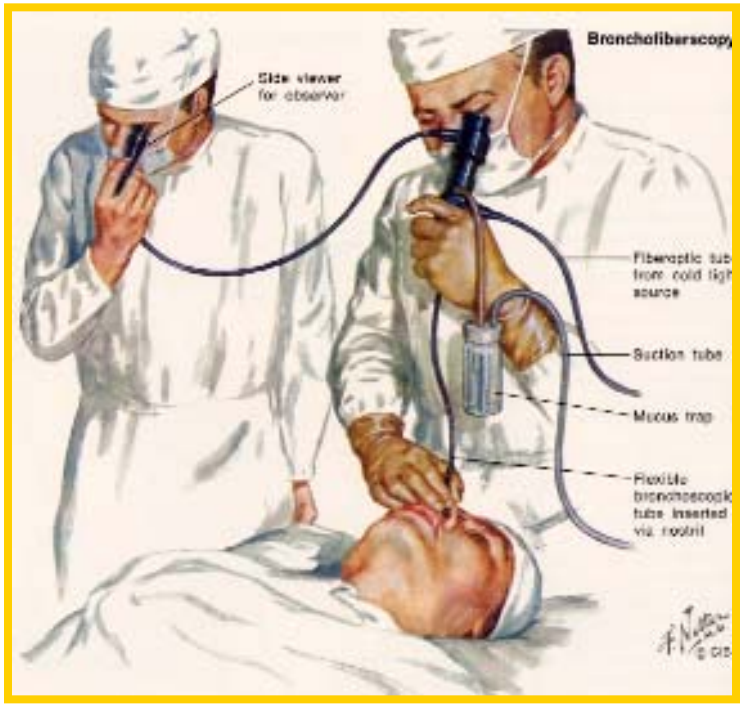


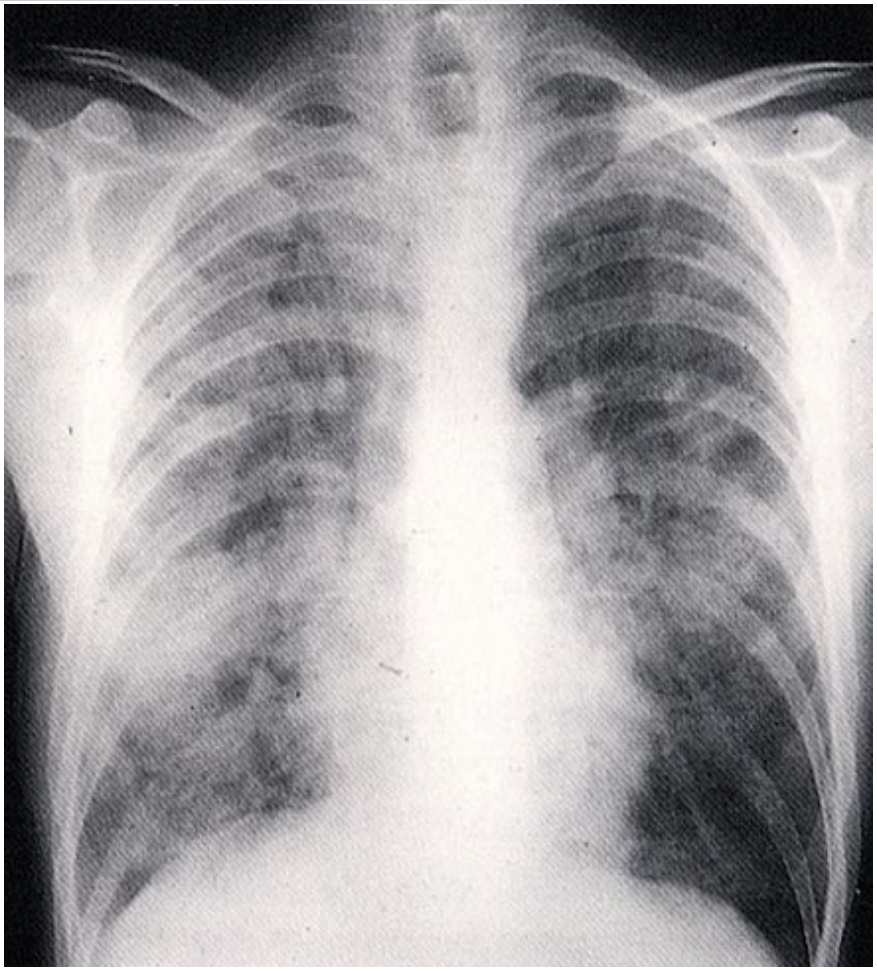
Treatment of PCP

- Standard treatment
  - First line TMP-SMX 5mg/kg 8 hourly X 21 days
  - Adjunctive corticosteroids
    - Prednisone
      - 40mg twice daily X 5 days
      - 40mg daily X 5 days
      - 20mg daily X 11 days

Pneumocystis carinii Pneumonia

- **General rule**: start presumptively based on initial evaluation and workup

- **Preferred TMP-SMX**
  - TMP 15mg/kg/day + SMX 75mg/kg/day po or IV in 3-4 divided doses
  - Can be given po (4 QID)
  - Treat for 21 days
  - Intolerance to TMP-SMX in 25 to >50% (rash, fever)



Role of corticosteroids in PCP

- Improved short-term mortality and progression to respiratory failure with moderate/severe PCP
- Adverse events: exacerbation of thrush, herpes (common); also steroid psychosis (rarer)

Alternatives for PCP therapy

- For **mild-moderate PCP** ($pO_2 \geq 70$):
  - Clindamycin + primaquine
  - TMP + dapsone
  - Atovaquone
  - Comparative trial (ACTG 108) found TMP-SMX, TMP-dapsone, clinda-primaquine equally effective[1]

1. Safrin et al, Annals Int Med, 1996

Prophylaxis

- TMP/SMX
  - 1 ds tablet daily or 3 X weekly
- Alternatives
  - Dapsone 100mg daily
  - Aerosolized pentamidine 300mg monthly
  - Atovaquone 1500mg daily

Discontinuing prophylaxis

- 2 trials confirm safety of discontinuing prophylaxis on HAART –*Lopez et al 2001 (NEJM), and Ledergerber et al 2001 (NEJM)*
  - CD4 >350 (? 200)
- Should not be stopped if:
  - Oral candidiasis
  - Ongoing weight loss
  - Corticosteroid or cytotoxic treatment
- Close monitoring of CD4 required

Other issues in PCP management

- When initiating PCP therapy, expect patient's respiratory status to worsen before it improves
- If sudden decompensation, R/O pneumothorax
- G6PD deficiency - may not tolerate high dose TMP-SMX, dapsone or primaquine
- Sulfa resistance - amino acid mutations in sulfa target enzyme associated with increased rate of prophylaxis failure[1] and poor response to treatment[2]

1. Kazanjian, et al. AIDS 1998 **2. Huang, et al. 6th CROI 1999**

Toxoplasma gondii

- Organism
  - *Toxoplasma gondii,* a protozoa
- Epidemiology and route of infection
  - Seroprevalence rate is 30% in USA compared with 90-100% in France and developing nations
  - Ingestion of oocysts or tissue cysts leads to the release of organisms which mature into tachyzoites which disseminate and then persist in the CNS or extraneural tissues as tissue cysts
  - Immunosuppression allows for the development of trophozoites from the tissue cysts leading to disease

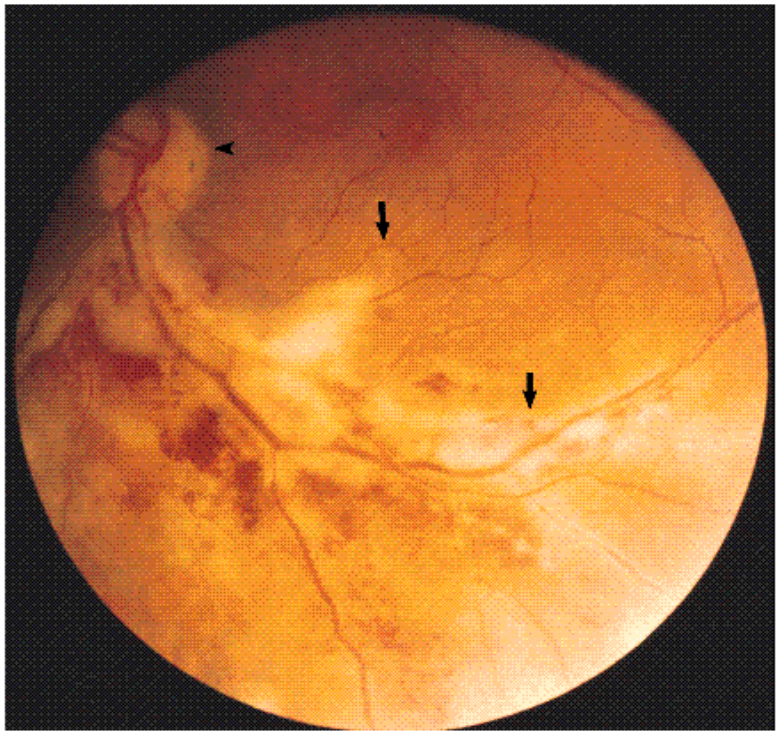

Toxoplasma gondii
?
CYSTS
OOCYSTS
OOCYSTS
CYSTS

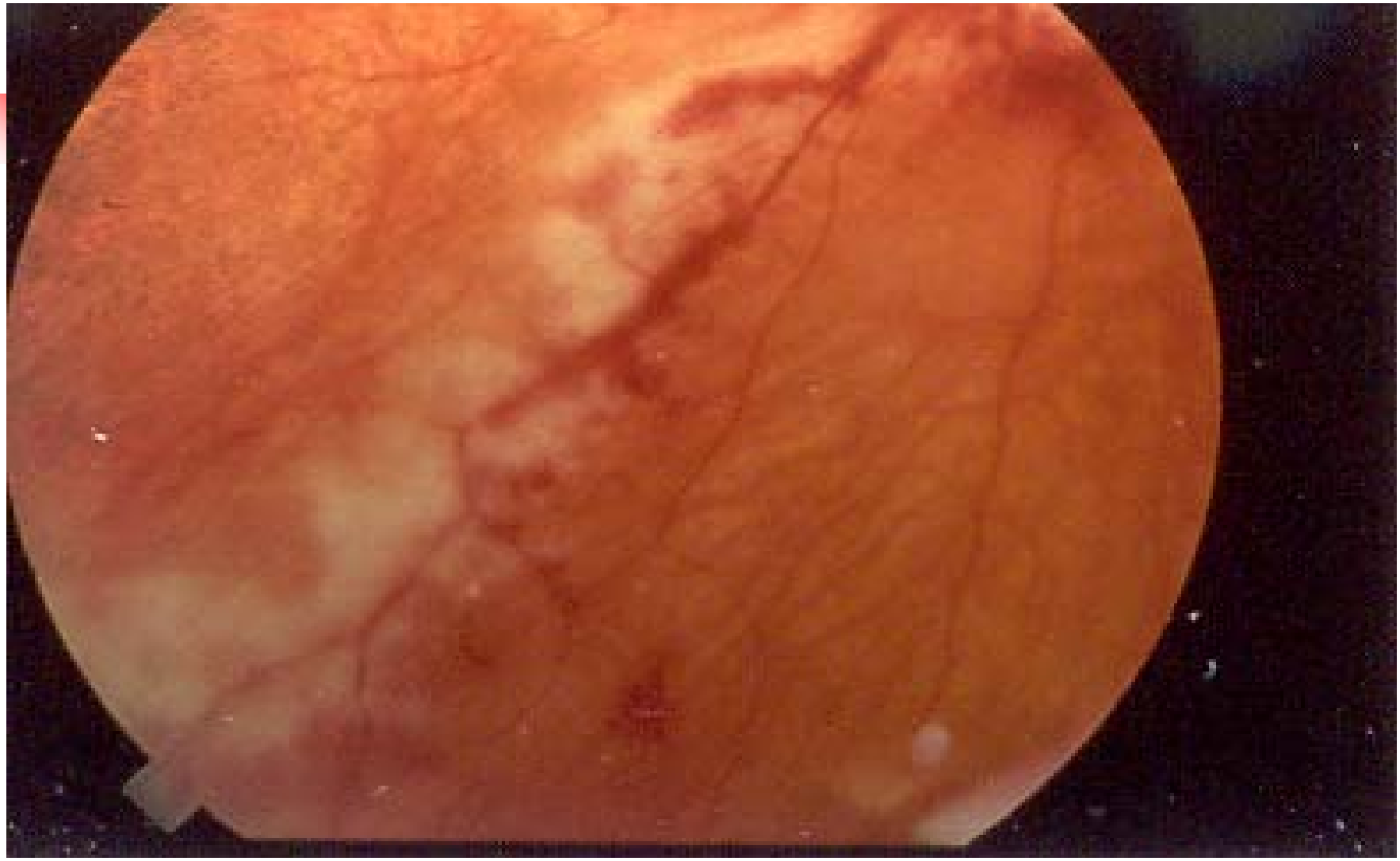
Toxoplasma gondii Diagnosis

- Serology (ELISA) is positive in over 95% of patients with Toxoplasma encephalitis
- MRI or contrast enhanced CT scans typically show multiple enhancing lesions in the gray-white matter junction, white matter or basal ganglia
- Definitive diagnosis requires brain biopsy but a presumptive diagnosis can be made given a characteristic presentation and response to anti-Toxoplasma therapy

Cytomegalovirus (CMV)

- Causes retinitis, GI disease, pulm dx and CNS disease syndromes
- Drugs used to treat CMV
  - Ganciclovir IV
  - Valganciclovir po
  - Foscarnet IV
  - Cidofovir IV





Clinical Presentation

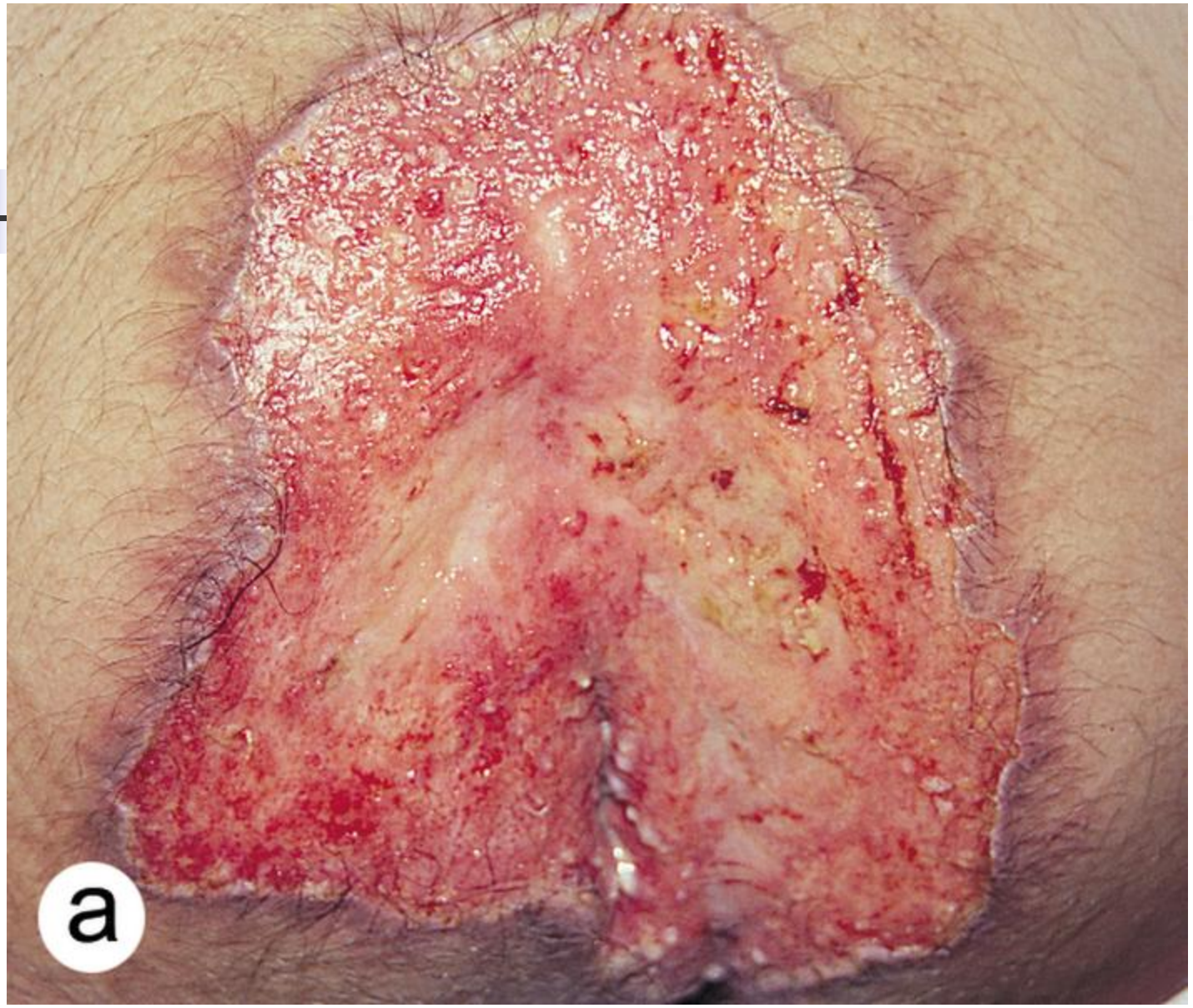
- member of the herpes virus family
- CD4 < 100
- Encephalitis; fever, mental status changes, headache, seizures and focal neurological signs

CMV Diagnosis

- Retinitis: by examination (pattern recognition)
- Gastrointestinal disease: Characteristic histopathology
- CNS disease: Periventricular or ependymal enhancement on MRI or CT scan in encephalitis or ventriculoencephalitis
- PCR of CSF very sensitive and specific

Herpes Zoster (Shingles)

- Dangerous if infection involves eye area (V1) or is disseminated (multiple dermatomes)
- Complications: scarring, post-herpetic neuralgia
- Treatment: high dose oral acyclovir, valacyclovir, or famciclovir
- Intravenous acyclovir for disseminated or severe disease
- Treat for at least 7 d (until lesions crust)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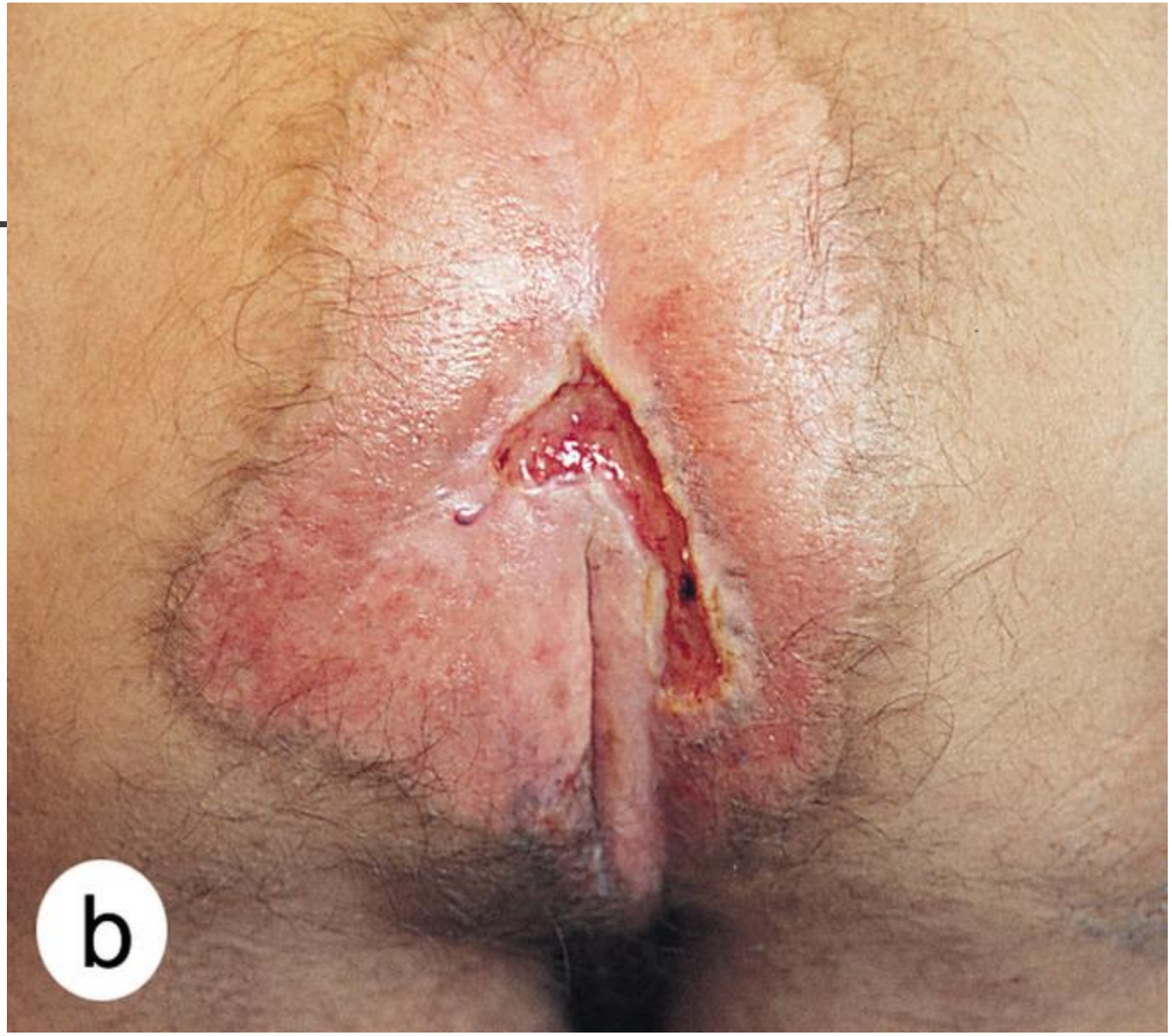
Herpes Simplex Virus (HSV)

- Patient given Acyclovir 400 mg 3 times daily for one week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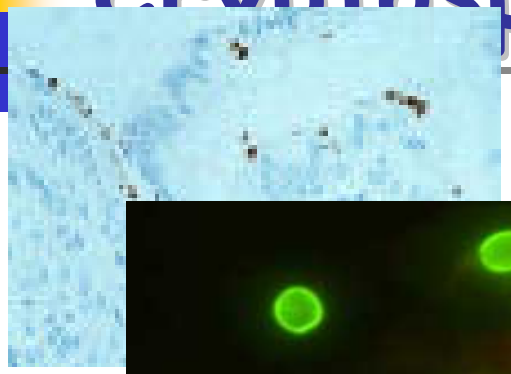
Diarrhea

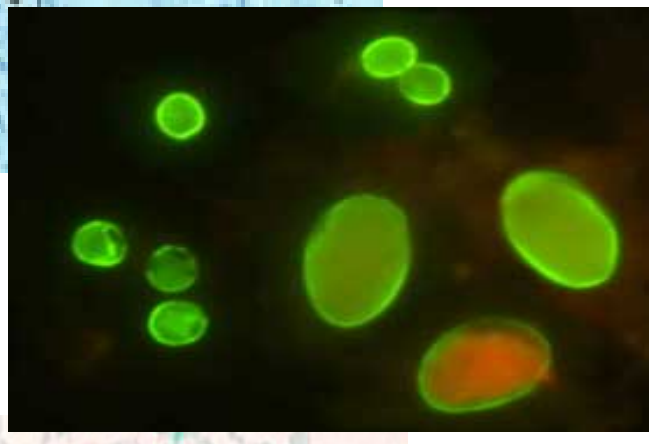
- Common problem
- Many possible causes, including pathogens found in non-HIV setting
  - **Salmonella, Shigella**
  - **Parasitic infections (Giardia, Entamoeba histolytica)**
- Cause of wasting
- Investigate vs empiric treatment
  - **Flagyl 400mg tds x 10 days**
  - **Ciprobay 500mg bd x 7 days**

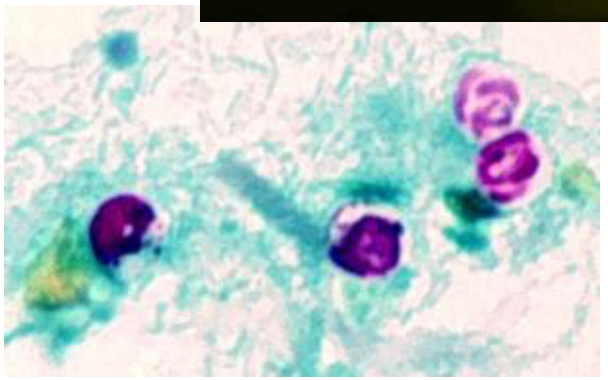
Diarrhea due to Protozoan Infections

- *Cryptosporidium*
- *Microsporidium*
- *Isospora*

Cryptosporidiosis







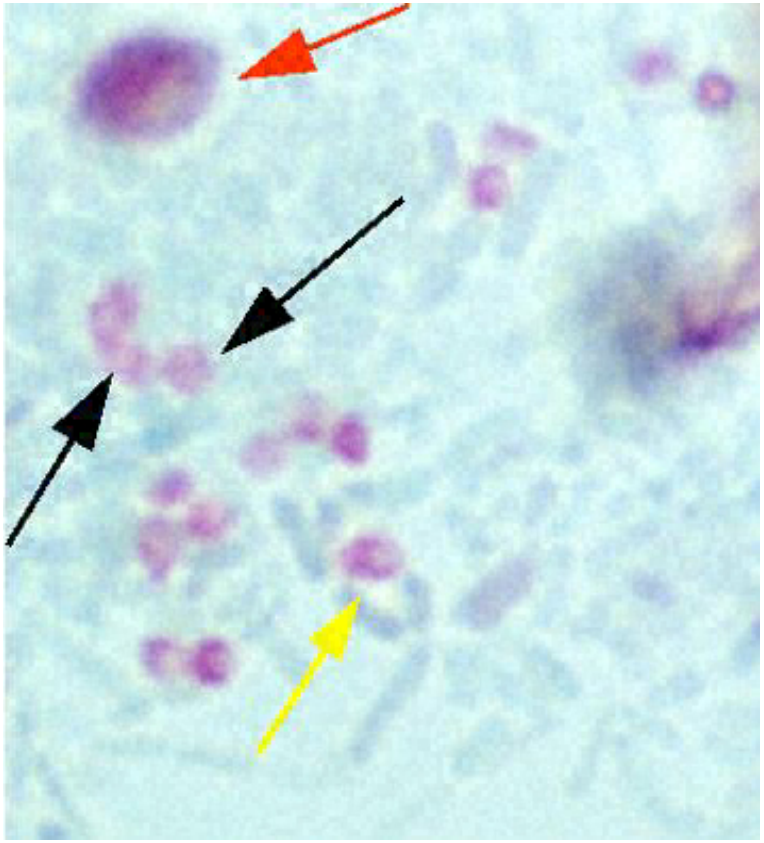
- Best treatment is ARVs
- Control of symptoms
  - Bulk stool with supplements
  - Anti-diarrheal agents

DPD www.cdc.gov

Chen et al, NEJM, May 2002

Microsporidiosis

- ARVs best treatment
- Albendazole 400-800mg po BID x ≥3 wks (*Septata intestinalis*)
- Fumagillin (NEJM 2002)
- Symptomatic treatment with nutritional supplements and antidiarrheals
- Only anecdotal benefit with itra, fluc, atavoquone, metronidazole



Isosporiasis

- Preferred
  - TMP-SMX 2 DS po bid
  - Treat for 2-4 wks
- Alternative
  - Pyrimethamine + folinic acid
  - 4 wks
- Suppressive
  - TMP-SMX 1-2 DS/d
  - Pyrimethamine +sulfadoxine